Neurological Symptoms Among US Diplomats in Cuba

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The primary value of publishing case reports and case series in the medical literature involves the documentation of symptoms, signs, and clinical data in a unique group of individuals. Often at the time of initial report, the fundamental etiology and pathophysiologic mechanism underlying the clinical phenomena are not yet fully understood, but the clear description of potentially pertinent data serves as a foundation on which other clinicians and investigators can build.

For example, in 1881, Wernicke described a syndrome of acute confusion, ophthalmoplegia, and ataxia and, in 1887, Korsakoff described a series of patients with predominantly anterograde amnesia. Yet, it was not until several years later (and after several additional cases were published) that the 2 conditions were recognized as part of a clinical syndrome—Wernicke-Korsakoff syndrome—often associated with chronic alcoholism.[1] The concept of vitamin deficiency was not well established at the time and the link between Wernicke-Korsakoff syndrome and thiamine deficiency was not determined until the 1930s,[1] illustrating that medical diagnosis at any given time depends to some extent on the current state of scientific knowledge, historical and cultural context, and the framework through which a disease is conceptualized.[2]

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In this issue of *JAMA*, Swanson et al[3] report a case series of 21 US government employees who were working in Havana, Cuba, from late 2016 to August 2017 and developed a variable constellation of neurological, otological, and ophthalmological signs and symptoms associated, in most cases, with preceding audible (n = 18) and other sensory (n = 12) phenomena. Coordinated multidisciplinary evaluation of the affected patients revealed that the most commonly reported symptoms were persistent sleep disturbance (n = 18), visual symptoms (n = 18), cognitive difficulty (n = 17), headache (n = 16), balance problems (n = 15), and auditory symptoms (n = 15). Physical examination and diagnostic testing abnormalities included reports of vestibular or balance dysfunction (n = 17), cognitive abnormalities (n = 16), eye movement abnormalities (n = 15), and moderate to severe sensorineural hearing loss (n = 3). Brain imaging showed nonspecific white matter changes in some individuals, but was otherwise unrevealing. Many of the individuals had prolonged symptoms that began to resolve over the course of months and, in many cases, after receiving rehabilitative therapies.

Several important considerations should guide interpretation of these data. First, although the patients were united to some extent by the common locations in which their symptoms first developed, there was some variability between patients in terms of the symptoms that each experienced. The precise time course over which each individual's symptoms evolved was not provided. Given that evaluations were conducted a mean of 203 days after onset, it remains unclear whether individuals who developed symptoms later were aware of the previous reports of others. Furthermore, the quantitative results for specific tests (eg, neuropsychological tests) are not yet available for all affected patients, so independent assessment as to the scope and severity of deficits among all individuals remains challenging.

The limitations often inherent in case series should also urge caution in interpreting the findings. The initial clinical evaluations were not standardized and examiners were not blinded, which is important given that several of the abnormalities reported in the article (eg, eye movement and balance dysfunction) were based on patient self-report[4] or involved at least some degree of subjective interpretation by the clinician performing the examination. The lack of baseline evaluations and the absence of a control group, although understandable given the nature of the case series design, complicate interpretation of the findings because many of the symptoms and signs reported occur in the general population and in individuals with other neurological illnesses. For example, the prevalence of convergence insufficiency (characterized by a decreased ability to move the eyes toward each other when attempting to focus on a near target), has been reported to range from 1% to 33% (with an average prevalence of around 5%) among healthy individuals.[5] Further, less-than-perfect scores on the Functional Gait Assessment (which were considered to be evidence of balance dysfunction in this case series) occur among asymptomatic community-living adults and scores decrease with increasing age.[6]

Although exposure to audible phenomena was a prominent complaint in this case series, in the absence of baseline audiologic data, a definitive conclusion cannot be reached as to whether the 3 cases of sensorineural hearing loss occurred as a result of this exposure. Moreover, lack of information about the age of the specific individuals affected and the presence of other risk factors for hearing loss—although understandable given the study design and the inability to report patient-level demographics—would be particularly important to help clarify whether these findings could have had a more conventional explanation.

Nonetheless, the similarities among the 21 cases merit consideration of a common medical, environmental, or psychological event as the potential cause. The symptoms

reported by the 21 individuals overlap with several symptoms that may be seen in patients with various neurological, ophthalmological, or otological conditions. The authors emphasize similarities to the symptoms seen in concussion, with the notable exception that the individuals in this case series did not experience physical head trauma, as is typical in concussion or other forms of traumatic brain injury. This raises the question of whether, in the absence of physical trauma, central nervous system injury may be sustained through exposure to sound or other phenomena.

Although loud sound can certainly cause aural injury, data as to whether high-intensity sound at audible (20-20 000 Hz) or inaudible low frequencies (ie, infrasound [1-20 Hz]) is capable of inducing long-lasting central nervous system symptoms are unclear.[7,8] Ultrasound (>20 000 Hz)—specifically high-intensity focused ultrasound—is known to induce heating and coagulative necrosis of brain tissue. This characteristic has recently been exploited to stereotactically and noninvasively produce focal lesions in the treatment of movement disorders.[9] However, the technical challenges in using ultrasound waves for nonlethal attacks include the rapid absorption of ultrasound by surrounding air and a requirement for close proximity to the source to induce injury.[7]

In any case, the analogy to concussion may be unnecessary as many of the symptoms described also occur in other medical, neurological, or psychiatric conditions. In particular, persistent postural-perceptual dizziness (PPPD) is a syndrome characterized primarily by chronic symptoms of dizziness and perceived unsteadiness, often triggered by acute or chronic vestibular disease, neurological or medical illness, or psychological distress.[10] Similar to the balance and vestibular symptoms reported by many of the patients in this case series, the symptoms of PPPD are classically exacerbated by walking, standing still, and exposure to complex visual environments. Abnormalities in balance and vestibular testing may also be seen in this condition and do not exclude the diagnosis, but rather can occur as nondiagnostic findings or point to an associated underlying cause.[11] Although the degree of similarity between PPPD, a disorder characterized as functional,[10] and the cases reported by Swanson and colleagues[3] is notable, PPPD alone does not appear to explain the entirety of the symptoms reported nor the clustering of individuals affected.

The occurrence of symptoms among individuals residing in close proximity recalls events such as the 1976 outbreak of Legionnaires disease among conference attendees at a hotel in Philadelphia, Pennsylvania,[12] a condition for which a common toxic exposure was considered and excluded before discovery that the syndrome was due to a pathogenic bacterium. However, Swanson et al[3] reasonably conclude that the available clinical data in this case series do not support an infectious etiology. The authors also raise the possibility of mass psychogenic illness but seem to dismiss it on the grounds that most of the affected individuals were motivated to return to work as soon as possible. However, it should be emphasized that in psychogenic (functional) illness (rather than malingering), individuals are not consciously motivated by primary and secondary gain.[13]

At this point, a unifying explanation for the symptoms experienced by the US government officials described in this case series remains elusive and the effect of possible exposure to audible phenomena is unclear. Going forward, it would be helpful for government employees traveling to Cuba to undergo baseline testing prior to deployment to allow for a more informed interpretation of abnormalities that might later be detected after a potential exposure. Just as critical, especially for assessment of individuals without baseline information, will be comparison of data with age- and sex-matched controls, and blinding of assessors to both patients and controls if possible. Additional testing with advanced neuroimaging techniques (especially compared with an age- and sex-matched control group) may also help characterize any functional or structural brain changes.

Given that scientific knowledge as well as the various frameworks through which this clinical condition might be understood or related to are dynamic and evolving,[14-16] it is of paramount importance that documentation of signs, symptoms, and other clinical data remains as objective as possible. Many potential causes for the symptoms experienced by the individuals in the case series, including known disease entities previously discussed or perhaps an etiology yet to be described, remain possibilities. Before reaching any definitive conclusions, additional evidence must be obtained and rigorously and objectively evaluated.

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REFERENCES

1. Victor M, Adams RD, Collins GH. *The Wernicke-Korsakoff Syndrome and Related Neurologic Disorders Due to Alcoholism and Malnutrition*. 2nd ed. Philadelphia, PA: F. A. Davis Co; 1989:1-10.

2. Day GS, Tang-Wai DF, Shamy MC. A case study in the history of neurology. *Neurohospitalist*. 2016;6 (4):181-184.

3. Swanson RL II, Hampton S, Green-McKenzie J, et al. Neurological manifestations among US government personnel reporting directional audible and sensory phenomena in Havana, Cuba [published February 15, 2018]. *JAMA*. doi:10.1001/jama.2018.1742

4. Stiebel-Kalish H, Amitai A, Mimouni M, et al. The discrepancy between subjective and objective measures of convergence insufficiency in whiplash-associated disorder versus control participants. *Ophthalmology*. 2018; S0161-6420(17)33033-6.

5. Cooper J, Jamal N. Convergence insufficiency-a major review. *Optometry*. 2012;83(4):137-158.

6. Walker ML, Austin AG, Banke GM, et al. Reference group data for the functional gait assessment. *Phys Ther*. 2007;87(11):1468-1477.

7. Rehn KW, Riggs PK. *Technical Document 3138: Non-Lethal Swimmer Neutralization Study*. San Diego, CA: SPAWAR Systems Center San Diego; 2002.

8. Jauchem JR, Cook MC. High-intensity acoustics for military nonlethal applications: a lack of useful systems. *Mil Med*. 2007;172(2):182-189.

9. Fishman PS, Frenkel V. Treatment of movement disorders with focused ultrasound. *J Cent Nerv Syst Dis*. 2017;9:1179573517705670.

10. Popkirov S, Staab JP, Stone J. Persistent postural-perceptual dizziness (PPPD): a common, characteristic and treatable cause of chronic dizziness. *Pract Neurol*. 2018;18(1):5-13.

11. Staab JP. Chronic subjective dizziness. *Continuum (Minneap Minn)*. 2012; 18(5 neuro-otology):1118-1141.

12. Office of the Associate Director for Science, Centers for Disease Control and Prevention. History, mystery, and discovery: 40 years of Legionnaires' disease. https://www.cdc.gov/od /science/wewerethere/legionnaires/index.html. Accessed February 6, 2018.

13. Lehn A, Gelauff J, Hoeritzauer I, et al. Functional neurological disorders: mechanisms and treatment. *J Neurol*. 2016;263(3):611-620.

14. Sharp DJ, Jenkins PO. Concussion is confusing us all. *Pract Neurol*. 2015;15(3):172-186.

15. Staab JP, Eckhardt-Henn A, Horii A, et al. Diagnostic criteria for persistent postural-perceptual dizziness (PPPD): consensus document of the committee for the Classification of Vestibular Disorders of the Bárány Society. *J Vestib Res*. 2017;27 (4):191-208.

16. Stone J. Neurologic approaches to hysteria, psychogenic and functional disorders from the late 19th century onwards. *Handb Clin Neurol*. 2016;139: 25-36.